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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,574	AUDONNET ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

The MAILING DATE of this communication appears on the cover sheet with the correspondence address.

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION

THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 13 January 2003 .

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 84-220 is/are pending in the application.

4a) Of the above claim(s) 119-220 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 84-118 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. ____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) Other: _____

DETAILED ACTION

1. This Action is in response to the communication filed on 1-13-03, as Paper No. 13. The amendment has been entered. Claims 1-83 have been cancelled. New claims 84-220 have been added. Claims 84-220 are currently pending in the application and are addressed herein.
2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Newly submitted claims 119-220 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 119-209 are drawn to non-elected species. Applicants elected the species BRSV vaccine, in the communication filed 7-29-02 (Paper No. 11). Furthermore, claims 210-220 are drawn to methods for inducing an immune response against a pathogen. Methods of inducing an immune response against a pathogen are distinct from vaccines (the originally presented invention) because 1) a vaccine is a product, while a method of inducing an immune response is a process of use; and 2) a vaccine is used to confer protective immunity in an animal, while a method of inducing an immune response merely indicates that an immune response is raised against a pathogen. Therefore, the product (a vaccine) can be used in a materially different process of use. Furthermore, the searches required for a vaccine and a method for inducing an immune response are not co-extensive, *prima facie* evidence of a serious search burden.

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Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 119-220 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 84-118 are examined herein.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 84-118 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5 and 16-19 of copending Application No. 09/766,442. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to a BRSV vaccine. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 84, 85, 96, 112, and 116-118 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine. As mentioned below, a DNA plasmid vaccine for BRSV was known in the prior art and the lipid complex DMRIE/DOPE was known to act as an adjuvant as well as a facilitator of DNA delivery into cells. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against a bovine pathogen comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding an immunogen of the bovine pathogen and a cationic lipid (see claims 84, 85, 112, 118); wherein the vaccine further comprises DOPE (claims 85, 112); wherein the bovine pathogen is BRSV (see claim 96); wherein the immunogen is BRSV-F (claim 116) or BRSV-G (claim 118).

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and -G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the

respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Audonnet and Klavinskis to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the increased expression of the encoded pathogens (here, BRSV-F and/or BRSV-G) and to stimulate the host's immune system in order to get an increased immune response against the pathogens.

4. Claims 84-91 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as

DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. However, GM-CSF was known to act as an adjuvant for vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 84 and 85 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus *in vivo*) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p. 132, under “A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as “a therapeutic agent treating

various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

5. Claims 84, 92, 94, 95, 100 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence

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of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the BRSV-F gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

6. Claims 84, 93, 97, 98 and 104 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition. Audonnet specifically teaches that the vaccine can comprise plasmid(s) which encode and express BRSV-F and/or BRSV-G.

Neither Audonnet nor Klavinskis teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal BRSV-F or NRSV-G signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

7. Claims 84-118 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1

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(Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine; the a gene encoding the BRSV-F gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; a second plasmid encoding the BRSV-G gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and -G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE

complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation.” (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Neither Audonnet nor Klavinskis teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus *in vivo*) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under “A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as “a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in

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reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Audonnet, Klavinskis, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Audonnet, Klavinskis, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the

tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, BRSV-F and/or BRSV-G) resulting in a greater degree of protective immunity to the pathogen.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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10. Claims 84, 85 and 118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of in view of in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine. As mentioned below, a DNA plasmid vaccine for BRSV was known in the prior art and the lipid complex DMRIE/DOPE was known to act as an adjuvant as well as a facilitator of DNA delivery into cells. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against a bovine pathogen comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding an immunogen of the bovine pathogen and a cationic lipid (see claims 84, 85, 112, 118); wherein the vaccine further comprises DOPE (claims 85, 112); wherein the bovine pathogen is BRSV (see claim 96); wherein the immunogen is BRSV-F (claim 116) or BRSV-G (claim 118).

Cox teaches a vaccine for a bovine pathogen (here, bovine herpesvirus 1) comprising a plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding a pathogenic polypeptide of bovine herpesvirus (e.g. see abstract).

Cox does not teach that the vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA

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and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Cox and Klavinskis to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the increased expression of the encoded pathogens (here, a bHSV-1 pathogen) and to stimulate the host's immune system in order to get an increased immune response against the pathogens

11. Claims 84-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. However, GM-CSF was known to act as an adjuvant for

vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 84 and 85 are obvious in view of the teachings of Cox and Klavinskis as mentioned above.

As mentioned above, Cox teaches a bovine plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Cox nor Klavinskis teach that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus *in vivo*) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under “A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as “a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be

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employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

12. Claims 84, 92, 94, 100 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (J. Virol. Vol. 67, pages 5664-5667; IDS reference AT) in view of in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen wherein the improvement comprises 1) the addition of a lipid complex (such as

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DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Cox and Klavinskis as mentioned above.

As mentioned above, Cox teaches a bovine HSV-1 plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Cox nor Klavinskis teach that the vaccine composition comprises a bovine pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the bHSV-1 gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

13. Claims 84, 93, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (J. Virol. Vol. 67: 5664-5667; 1993; IDS # AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Cox and Klavinskis as mentioned above.

As mentioned above, Cox teaches a bovine HSV-1 plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Cox nor Klavinskis teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of the pathogen.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal bHSV-1 pathogen signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

14. Claims 84-95, 100-111 and 118 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (J. Virol. Vol. 67: 5664-5667; 1993; IDS # AT) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to

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the vaccine; the a gene encoding the pathogen with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Cox teaches a vaccine for bovine HSV-1 comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding bHSV-1 glycoproteins (e.g., see abstract).

Cox does not teach that the vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, “Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation.” (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Neither Audonnet nor Klavinskis teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

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Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus *in vivo*) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under “A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as “a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression.” (See column 1, lines 41-53).

Cox, Klavinskis, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted

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form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Cox, Klavinskis, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, bovine HSV-1 glycoproteins) resulting in a greater degree of protective immunity to the pathogen.

Response to Arguments

15. Applicant's arguments with respect to claims drawn only to a vaccine for any farm animal have been considered but are moot in view of the claim amendments limiting the vaccine to a bovine vaccine. However, the new claims have been rejected as set forth above.

16. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

17. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the suggestion to combine is present in the prior art. For example, the prior art clearly indicates that each of the modifications encompassed by the instant claims can be used to make a better, more efficacious immune response to a pathogen, thus resulting in a better,

more efficacious vaccine. Furthermore, a bovine DNA vaccine comprising plasmid(s), which encode and express the BRSV-F and/or BRSV-G gene was known in the art (Audonnet). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art make all of the known modifications to the known DNA vaccine in order to make a better, more efficacious vaccine.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
March 24, 2003